

§ 1.136(a), and any fees required therefor (including fees for net addition of claims) are hereby authorized to be charged to our Deposit Account No. 19-0036.

*Amendments*

*In the Claims:*

Please substitute the following claims 1, 46, 59, 76 and 78 for the pending claims 1, 46, 59, 76 and 78:

1. (Twice amended) A pharmaceutical composition, comprising:

(a) a polypeptide comprising Ser (69) - Ser (208) of SEQ ID NO:2 in a concentration range of about 0.02 to about 40 mg/ml (w/v);

(b) a buffer having a buffering capacity of about pH 5.0 to about pH 8.0 at a concentration range of about 5 mM to about 50 mM;

(c) a pharmaceutically acceptable diluent to bring the composition to a designated volume; and

(d) a preservative selected from the group consisting of m-cresol, chlorobutanol, and a mixture of methyl paraben and propyl paraben.

B<sub>2</sub> 50  
46. (Once amended) The pharmaceutical composition of claim <sup>48</sup>44, wherein said etherified cellulose is methylcellulose, hydroxyethyl cellulose, hydroxy propyl cellulose, hydroxy propyl methylcellulose, or carboxymethyl cellulose.

~~56~~  
59.

(Once amended)

~~55~~  
58.

The composition of claim 58, wherein said gel forming

agent is (1) a vinyl polymer selected from the group consisting of polyacrylic acid, polymethacrylic acid, polyvinyl pyrrolidone polyvinyl alcohol, and salts and esters thereof; or (2) a polysaccharide selected from the group consisting of a cellulose derivative, a glycosaminoglycan, agar, pectin, alginic acid, dextran,  $\alpha$ -amylose, amylopectin, chitosan, and salts or esters thereof.

~~70~~  
76.

(Twice amended)

A pharmaceutical composition comprising:

(a) about 3.3 mg/ml of a polypeptide comprising Ser (69) - Ser (208) of

SEQ ID NO:2;

(b) 10 mM sodium citrate

(c) 20 mM sodium chloride;

(d) 1 mM EDTA

(e) 2% w/v glycine;

(f) 0.5% w/v sucrose; and

(g) water;

wherein the composition is at a pH of about 6.2.

~~73~~  
78.

(Twice amended)

A pharmaceutical composition comprising:

(a) about 1.0 mg/ml of a polypeptide comprising Ser (69) - Ser (208) of

SEQ ID NO:2;

(b) 10 mM sodium citrate;

(b) 0.46% hydroxyethylcellulose;

- DS  
C&A
- (c) 7% sucrose;
  - (d) 20 mM sodium citrate;
  - (e) 20 mM sodium chloride; and
  - (f) 1 mM EDTA;

wherein the composition is at a pH of about 6.2.

[ Please add the following new claims: ]

75  
82.

BP (New) A pharmaceutical composition produced by the process of admixing:

- (a) a polypeptide comprising Ser (69) - Ser (208) of SEQ ID NO:2 in a concentration range of about 0.02 to about 40 mg/ml (w/v);
- (b) a buffer having a buffering capacity of about pH 5.0 to about pH 8.0 at a concentration range of about 5 mM to about 50 mM;
- (c) a pharmaceutically acceptable diluent to bring the composition to a designated volume; and
- (d) a preservative selected from the group consisting of m-cresol, chlorobutanol, and a mixture of methyl paraben and propyl paraben.

76  
83.

(New) The pharmaceutical composition of claim <sup>75</sup>82, further comprising one

or more of:

- (a) a chelating agent at a concentration range of about 0 mM to about 10 mM; and
- (b) a tonicifier at a concentration range of about 0 mM to about 150 mM.

~~77~~  
~~84.~~ (New) The pharmaceutical composition of claim ~~83~~<sup>74</sup>, wherein said tonicifier is selected from the group consisting of NaCl, glycine, sucrose, mannitol, and mixtures thereof.

~~80~~  
~~85.~~ (New) The pharmaceutical composition of claim ~~82~~<sup>75</sup>, further comprising one of:

- 34  
cont.
- (a) about 0.5% to about 2% w/v glycerol,
  - (b) about 0.1% to about 1% w/v methionine, or
  - (c) about 0.1% to about 2% w/v monothioglycerol.

~~81~~  
~~86.~~ (New) The pharmaceutical composition of claim ~~82~~<sup>76</sup>, wherein said polypeptide is present in a concentration range of about 0.05 to about 30 mg/ml (w/v).

~~82~~  
~~87.~~ (New) The pharmaceutical composition of claim ~~86~~<sup>81</sup>, wherein said polypeptide is present in a concentration range of about 0.1 to about 20 mg/ml (w/v).

~~83~~  
~~88.~~ (New) The pharmaceutical composition of claim ~~87~~<sup>82</sup>, wherein said polypeptide is present in a concentration range of about 0.2 to 4 mg/ml (w/v).

~~84~~  
~~89.~~ (New) The pharmaceutical composition of claim ~~82~~<sup>75</sup>, wherein said diluent is water.

~~78~~  
~~90.~~ (New) The pharmaceutical composition of claim ~~76~~  
~~83~~, wherein said chelating agent is EDTA at a concentration of about 1 mM, and said tonicifier is present at a concentration of about 125 mM.

~~83~~  
~~91.~~ (New) The pharmaceutical composition of claim ~~75~~  
~~82~~, wherein said pH is from about pH 5.5 to about pH 6.5.

~~86~~  
~~92.~~ (New) The pharmaceutical composition of claim ~~85~~  
~~91~~, wherein said pH is about pH 6.0.

~~87~~  
~~93.~~ (New) The pharmaceutical composition of claim ~~75~~  
~~82~~, wherein said buffer is selected from the group consisting of phosphonic, acetic, aconitic, citric, glutaric, malic, succinic carbonic acid, and an alkali or alkaline earth salt thereof.

~~88~~  
~~94.~~ (New) The pharmaceutical composition of claim ~~87~~  
~~93~~, wherein said buffer is a phosphate, acetate or citrate salt.

~~89~~  
~~95.~~ (New) The pharmaceutical composition of claim ~~87~~  
~~93~~, wherein said buffer is a citrate salt.

~~90~~  
~~96.~~ (New) The pharmaceutical composition of claim ~~75~~  
~~82~~, wherein said buffer is present in a concentration range of about 5 mM to about 30 mM.

~~91~~ (New) The pharmaceutical composition of claim ~~90~~<sup>70</sup>, wherein said buffer is a citrate salt present in a concentration of from about 10 mM to about 20 mM.

~~92~~<sup>98</sup> (New) The pharmaceutical composition of claim ~~82~~<sup>75</sup>, further comprising a stabilizing amount of one or more of (a) an antioxidant or (b) a thiol-compound.

~~93~~<sup>99</sup> (New) The pharmaceutical composition of claim ~~82~~<sup>75</sup>, wherein said composition is maintained at a temperature at or below -20°C.

B<sub>4</sub>  
~~94~~<sup>100</sup> (New) The pharmaceutical composition of claim ~~82~~<sup>75</sup>, wherein said polypeptide is selected from the group consisting of: (i) Ser (69) - Ser (208) of SEQ ID NO:2; (ii) Ser (69) - Ser (208) of SEQ ID NO:2 with a methionine at the N-terminus; and (iii) a mixture of (i) and (ii).

~~95~~<sup>101</sup> (New) The pharmaceutical composition of claim ~~82~~<sup>75</sup>, further comprising a bulking agent.

~~109~~<sup>102</sup> (New) The pharmaceutical composition of claim ~~101~~<sup>95</sup>, wherein said bulking agent is selected from the group consisting of sucrose, glycine, mannitol, trehalose, and mixtures thereof.

~~112~~<sup>103</sup> (New) The pharmaceutical composition of claim ~~102~~<sup>109</sup>, wherein said bulking agent is sucrose or a mixture of sucrose and glycine.

~~78~~  
104. (New) The pharmaceutical composition of claim ~~83~~<sup>76</sup>, further comprising a bulking agent.

~~111~~  
105. (New) The pharmaceutical composition of claim ~~102~~<sup>109</sup>, wherein said bulking agent is present in a concentration of about 2% to about 10% w/v.

~~110~~  
106. (New) The pharmaceutical composition of claim ~~102~~<sup>109</sup>, wherein said bulking agent is 5% mannitol, 7% sucrose, 8% trehalose, or 2% glycine + 0.5% sucrose.

~~94~~  
107. (New) The pharmaceutical composition of claim ~~101~~<sup>95</sup>, wherein said pH is about pH 6.2.

~~97~~  
108. (New) The pharmaceutical composition of claim ~~101~~<sup>95</sup>, wherein said diluent is water.

~~101~~  
109. (New) The pharmaceutical composition of claim ~~101~~<sup>95</sup>, wherein said buffer is selected from the group consisting of phosphonic, acetic, aconitic, citric, glutaric, malic, succinic carbonic acid, and an alkali or alkaline earth salt thereof.

~~102~~  
110. (New) The pharmaceutical composition of claim ~~109~~<sup>101</sup>, wherein said buffer is a phosphate or citrate salt.

<sup>103</sup>  
~~111.~~ (New) The pharmaceutical composition of claim <sup>102</sup>~~110~~, wherein said buffer is a citrate salt.

<sup>98</sup>  
~~112.~~ (New) The pharmaceutical composition of claim <sup>97</sup>~~108~~, wherein over 90% of the water is removed by lyophilization.

<sup>99</sup>  
~~113.~~ (New) The pharmaceutical composition of claim <sup>98</sup>~~112~~, which is reconstituted in with an amount of sterile water effective to maintain isotonic conditions of about 290 mOsm.

<sup>104</sup>  
~~114.~~ (New) The pharmaceutical composition of claim <sup>95</sup>~~101~~, wherein said buffer is added in a concentration from about 5 mM to about 50 mM.

<sup>105</sup>  
~~115.~~ (New) The pharmaceutical composition of claim <sup>104</sup>~~114~~, wherein said buffer is citrate at a concentration of about 10 mM.

<sup>106</sup>  
~~116.~~ (New) The pharmaceutical composition of claim <sup>95</sup>~~101~~, further including a stabilizing amount of one or more of (g) an antioxidant, or (h) a thiol-compound.

<sup>100</sup>  
~~117.~~ (New) The pharmaceutical composition of claim <sup>98</sup>~~112~~, wherein said composition is reconstituted in sterile water containing a stabilizing amount of an antioxidant comprising: a) about 0.01% to about 2% w/v monothioglycerol, b) about 0.01%



to about 2% w/v ascorbic acid, c) about 0.01% to about 2% w/v methionine or d) combinations thereof.

<sup>113</sup>  
~~118~~. (New) The pharmaceutical composition of claim <sup>75</sup>~~82~~, further comprising a thickening agent in an amount effective to raise the viscosity to about 50 to about 10,000 cps.

*B*  
*cont*  
<sup>114</sup>  
~~119~~. (New) The pharmaceutical composition of claim <sup>113</sup>~~118~~, wherein said thickening agent is present in an amount effective to raise the viscosity to about 50 to about 1,000 cps.

<sup>115</sup>  
~~120~~. (New) The pharmaceutical composition of claim <sup>114</sup>~~119~~, wherein said thickening agent in an amount effective to raise the viscosity to about 200 to about 300 cps.

121. (New) The pharmaceutical composition of claim <sup>75</sup>~~118~~, wherein said thickening agent is present in a concentration of 0 to 5% (w/w).

122. (New) The pharmaceutical composition of claim <sup>75</sup>~~118~~, wherein said thickening agent is a water soluble etherified cellulose or a carbomer.

<sup>124</sup>  
~~123~~. (New) The pharmaceutical composition of claim 122, wherein said etherified cellulose is an alkyl cellulose, hydroxyalkyl cellulose, carboxyalkyl cellulose or alkylhydroxyalkyl cellulose.

<sup>123</sup>  
~~124.~~ (New) The pharmaceutical composition of claim 122, wherein said etherified cellulose is methylcellulose, hydroxyethyl cellulose, hydroxy propyl cellulose, hydroxy propyl methylcellulose, or carboxymethyl cellulose.

<sup>124</sup>  
~~125.~~ (New) The pharmaceutical composition of claim <sup>123</sup>~~124~~, wherein said etherified cellulose derivative has a molecular weight of about 50,000 to about 700,000 and is present in a concentration of about 0 to about 20% by weight.

<sup>125</sup>  
~~126.~~ (New) The pharmaceutical composition of claim <sup>124</sup>~~125~~, wherein said etherified cellulose derivative has a molecular weight of about 80,000 to about 240,000 and is present in a concentration of about 2% to about 8% by weight.

<sup>116</sup>  
~~127.~~ (New) The pharmaceutical composition of claim <sup>115</sup>~~120~~, wherein said buffer is citrate in a concentration of about 10 mM to about 50 mM.

<sup>117</sup>  
~~128.~~ (New) The pharmaceutical composition of claim <sup>116</sup>~~127~~, wherein said buffer is citrate in a concentration of about 10 mM to about 20 mM citrate.

<sup>118</sup>  
~~129.~~ (New) The pharmaceutical composition of claim <sup>116</sup>~~127~~, wherein said bulking agent is sucrose in a concentration of about 0.01% to about 5% sucrose.

<sup>119</sup>  
~~130.~~ (New) The pharmaceutical composition of claim <sup>118</sup>~~129~~, wherein said thickening agent is added directly to a liquid formulation and thereafter lyophilized.

<sup>120</sup>  
~~131.~~ (New) The pharmaceutical composition of claim <sup>118</sup>~~129~~, wherein said thickening agent is added to a lyophilized formulation by reconstituting said formulation by adding a suitable diluent having a thickening agent dissolved therein.

<sup>107</sup>  
~~132.~~ (New) The pharmaceutical composition of claim <sup>95</sup>~~101~~, further comprising a thickening agent in an amount effective to raise the viscosity to about 50 to about 10,000 cps.

<sup>127</sup>  
~~133.~~ (New) The composition of claim <sup>75</sup>~~82~~, further comprising a gelling agent in an amount effective to raise the viscosity to about 0.1 to about 10,000 cps at room temperature.

<sup>108</sup>  
~~134.~~ (New) The composition of claim <sup>95</sup>~~101~~, further comprising a gelling agent in an amount effective to raise the viscosity to about 0.1 to about 10,000 cps at room temperature.

<sup>128</sup>  
~~135.~~ (New) The composition of claim <sup>127</sup>~~133~~, wherein said gel forming agent is a water-soluble polymer capable of forming a viscous aqueous solution, or non-water soluble, water-swellaible polymer capable of forming a viscous solution.

<sup>129</sup>  
~~136.~~ (New) The composition of claim <sup>128</sup>~~135~~, wherein said gel forming agent is a high molecular weight polymer selected from the group consisting of vinyl polymer,

polyoxyethylene-polyoxypropylene copolymer, polysaccharide, protein, poly(ethylene oxide), acrylamide polymer or a salt thereof.

<sup>130</sup>  
~~127.~~ (New) The composition of claim ~~126~~<sup>129</sup>, wherein said gel forming agent is (1) a vinyl polymer selected from the group consisting of polyacrylic acid, polymethacrylic acid, polyvinyl pyrrolidone polyvinyl alcohol, and salts and esters thereof; or (2) a polysaccharide selected from the group consisting of a cellulose derivative, a glycosaminoglycan, agar, pectin, alginic acid, dextran,  $\alpha$ -amylose, amylopectin, chitosan, and salts or esters thereof.

<sup>131</sup>  
~~128.~~ (New) The composition of claim ~~126~~<sup>129</sup>, wherein said gel forming agent is a glycosaminoglycan selected from the group consisting of hyaluronic acid, chondroitin, chondroitin-4-sulfate, heparan sulfate, heparin and salts and esters thereof.

<sup>132</sup>  
~~129.~~ (New) The composition of claim ~~126~~<sup>131</sup>, wherein said glycosaminoglycan is present in combination with collagen, gelatin, or fibronectin.

<sup>133</sup>  
~~140.~~ (New) The composition of claim ~~126~~<sup>129</sup>, wherein said gel forming agent is an acrylamide polymer selected from the group consisting of a polyacrylamide or a polymethacrylamide.

<sup>134</sup>  
~~141.~~ (New) The composition of claim ~~126~~<sup>128</sup>, wherein said gel forming agent is a polyoxyethylene-polyoxypropylene block copolymer.

~~135~~  
~~142.~~ (New) The composition of claim ~~141~~<sup>134</sup>, which comprises about 10 to about 60% by weight of a polyoxyethylene-polyoxypropylene block copolymer having an average molecular weight of about 500 to 50,000.

~~136~~  
~~143.~~ (New) The composition of claim ~~142~~<sup>135</sup>, which comprises about 14 to about 18% by weight of a polyoxyethylene-polyoxypropylene block copolymer having a molecular weight in the range 1,000 to 15,000.

~~137~~  
~~144.~~ (New) The pharmaceutical composition of claim ~~82~~<sup>75</sup>, wherein said polypeptide is present in a concentration range of about 0.01 mg/ml to about 10 mg/ml (w/v).

~~138~~  
~~145.~~ (New) The pharmaceutical composition of claim ~~82~~<sup>75</sup>, further comprising one of:

- (a) lysine;
  - (b) hydroxypropyl- $\beta$ -cyclodextrin; and
  - (c) sulfated- $\beta$ -cyclodextrin;
- or combinations thereof.

~~139~~  
~~146.~~ (New) The pharmaceutical composition of claim ~~82~~<sup>75</sup>, wherein said preservative is a mixture of methyl paraben and propyl paraben.

~~147~~<sup>140</sup>. (New) The pharmaceutical composition of claim ~~146~~<sup>139</sup>, wherein said composition comprises 0.18% methyl paraben and 0.02% propyl paraben.

~~148~~<sup>141</sup>. (New) A pharmaceutical composition produced by the process of admixing:

- (a) about 1.0 mg/ml of a polypeptide comprising Ser (69) - Ser (208) of SEQ ID NO:2;
- (b) 20mM citrate, pH 5-5.5; and
- (c) 0.01% polysorbate 80.

~~149~~<sup>142</sup>. (New) The pharmaceutical composition of claim ~~148~~<sup>141</sup>, further comprising 1 mM EDTA.

~~150~~<sup>143</sup>. (New) The pharmaceutical composition of claim ~~148~~<sup>141</sup>, wherein said polypeptide is selected from the group consisting of: (i) Ser (69) - Ser (208) of SEQ ID NO:2; (ii) Ser (69) - Ser (208) of SEQ ID NO:2 with a methionine at the N-terminus; and (iii) a mixture of (i) and (ii).

~~151~~<sup>144</sup>. (New) A pharmaceutical composition produced by the process of admixing:

- (a) about 3.3 mg/ml of a polypeptide comprising Ser (69) - Ser (208) of SEQ ID NO:2;
- (b) 10 mM sodium citrate
- (c) 20 mM sodium chloride;
- (d) 1 mM EDTA

- (e) 2% w/v glycine;
- (f) 0.5% w/v sucrose; and
- (g) water;

wherein the composition is at a pH of about 6.2.

*145*  
~~152.~~ (New) The pharmaceutical composition of claim ~~151~~, wherein over 90% of the water is removed by lyophilization.

*146*  
~~153.~~ (New) The pharmaceutical composition of claim ~~151~~, wherein said polypeptide is selected from the group consisting of: (i) Ser (69) - Ser (208) of SEQ ID NO:2; (ii) Ser (69) - Ser (208) of SEQ ID NO:2 with a methionine at the N-terminus; and (iii) a mixture of (i) and (ii).

*147*  
~~154.~~ (New) A pharmaceutical composition produced by the process of admixing:

(a) about 1.0 mg/ml of a polypeptide comprising Ser (69) - Ser (208) of SEQ ID NO:2;

- (b) 10 mM sodium citrate;
- (b) 0.46% hydroxyethylcellulose;
- (c) 7% sucrose;
- (d) 20 mM sodium citrate;
- (e) 20 mM sodium chloride; and
- (f) 1 mM EDTA;

wherein the composition is at a pH of about 6.2.

<sup>148</sup>  
~~155~~. (New) The pharmaceutical composition of claim <sup>147</sup>  
~~154~~, wherein said  
polypeptide is selected from the group consisting of: (i) Ser (69) - Ser (208) of SEQ ID  
NO:2; (ii) Ser (69) - Ser (208) of SEQ ID NO:2 with a methionine at the N-terminus; and  
(iii) a mixture of (i) and (ii).

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